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Is this the end of intensified insulin therapy and obesity in light of updates with novel medicines?

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ABSTRACT

Aim: Modern times witness an increased prevalence of obesity and diabetes mellitus. While patients are offered a plan for blood glucose regulation, possible obesity issues, unfortunately, remain ignored. Blood glucose regulation inevitably deteriorates over time in diabetic patients that gradually gain weight.

Material and Method: We recruited 42 diabetic patients who applied to our internal medicine outpatient clinic to investigate the impacts of two new generation therapies, sodium-glucose co-transporter-2 inhibitor (SGLT-2i) and glucagon-like peptide-1 receptor agonist (GLP1-RA), on weight. Six patients were excluded from follow-up for various reasons, and the study was finalized with 36 patients. The patients were followed up regarding body mass index (BMI), HbA1c levels, and insulin cessation or dose reduction.

Results: We stopped insulin in 20 of 36 patients who started to receive SGLT-2i and GLP1-RA, while the insulin dose was reduced in the remaining patients. While the mean basal HbA1c level of the first group with insulin cessation was 9.13% (min-max: 6.4-14), it was recorded as 7.63% (min-max: 5, 2-10,8) in the sixth month of treatment modification ($p < 0.001$). Despite a slight HbA1c increase in two patients, we concluded a significant decrease in HbA1c levels in 18 patients. Altogether, these 20 patients experienced an average of 1.5% HbA1c reduction. The findings also revealed that the mean basal BMI value (38.99 kg/m²; min-max: 33.2-43.4) among these 20 patients significantly decreased to 38.13 kg/m² (0.86 kg/m²) in the sixth month of treatment modification. Among eight patients with reduced insulin and HbA1c level, the mean BMI value changed from 43.05 kg/m² (min-max: 38.3-52.5) to 40.91 (min-max: 38.1-50) at the sixth-month follow-up. In this case, we may assert that losing weight has a positive impact on blood glucose regulation. However, it changed from 34.87 kg/m² (min-max: 30.6-38.2) to 35.77 kg/m² (min-max: 31. 8-39.1) among the other eight patients with reduced insulin but unreduced HbA1c.

Conclusion: Overall, we believe that SGLT-2i and GLP1-RA, with significant benefits in both cardiovascular protection and weight control, would be more advantageous when used more frequently in obese patients without obvious contraindications since they rarely cause hypoglycemia and are easily tolerated.

Keywords: Type 2 diabetes mellitus, novel therapies, sodium glucose co-transporter-2 inhibitors, glucagon-like peptide-1 agonists

INTRODUCTION

Considered by definition, diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to the metabolic impact of insulin or defects in its secretion. Due to developing hyperglycemia, it then causes significant loss of function and failure in various organs and systems, particularly in the heart, kidneys, eyes, and vascular and nervous systems (1). The 2022 data from the International Diabetes Federation suggests that the world hosts about 537 million adult diabetes patients (2). DM is often considered in three types (type 1, type 2, and gestational diabetes) and presents with monogenic and secondary diabetes types despite a smaller frequency (3). Type 2 DM (T2DM) occurs due to beta cell dysfunction. In the early period, an abnormal increase emerges in insulin secretion that accounts for regulating glucose levels. Over time, decreased insulin secretion cannot maintain the glucose balance, which leads to hyperglycemia. Besides, the majority of patients suffer from central (abdominal) obesity (4).

Increased non-esterified fatty acids, hormones, and pro-inflammatory cytokines in obese individuals contribute to insulin resistance. Then, DM occurs with the addition of insulin resistance to the decreased pancreatic β-cell reserve (5). Individuals developing insulin resistance bear fluctuations in insulin levels and lower hepatic

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clearance than insulin-susceptible individuals. β-cells constantly communicate with insulin-susceptible tissues. Glucose demand of muscles, fat, and liver leads to increased insulin levels in β-cells, and any impairment in this communication paves the way for DM (6).

With its increasing frequency, T2DM has become a significant burden on the healthcare system in our country. The accelerated frequency of obesity and prediabetes has also raised concerns about addressing the subject. For those with predominant coronary artery disease, hypertension, or chronic renal disease, the best option for a second agent is a sodium-glucose co-transporter-2 inhibitor (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP1-RA), which demonstrate cardiovascular (CV) risk reduction, following the assessments of drug-specific and patient-related factors (7).

Since many efficient medicines are available in obesity management, healthcare providers may need to consider the weight-related impacts of each medicine when suggesting regimens. Agents associated with varying degrees of weight loss include metformin, α-glucosidase inhibitors, SGLT-2i, GLP1-RA, and amylin mimetics. While dipeptidyl peptidase-4 (DPP-4) inhibitors are neutral in weight, insulin secretagogues, thiazolidinediones, and insulin are frequently reported to be associated with weight gain (8, 9).

Uneda et al. (10) included 102,728 patients from 12 studies in their meta-analysis and found that GLP-1 RAs and SGLT2s significantly reduced the risk of major cardiovascular events (MACE) versus placebo in T2DM patients with obesity. This and similar studies also acknowledge these therapies in this period when every medicine is no longer released without a CV safety study.

While lifestyle modification-based weight loss strategies are initially successful, most become ineffective in the long run. Moreover, there is a growing need to consider pharmacological approaches to aid weight loss in diabetes-obesity. While old-fashioned glucose-lowering agents may cause weight gain, novel medicines, particularly SGLT-2i and GLP-1RA, simultaneously target weight loss and glycemic control (11-13).

SGLT-2i and GLP-1 RA effectively reduce HbA1c, but very different mechanisms make them an efficient duet for combination therapy. Recently, medicines in both antidiabetic classes have been shown to reduce CV events, most likely by different mechanisms. SGLT-2i exerts CV protective properties through hemodynamic effects, while GLP-1RA operates via anti-atherogenic/anti-inflammatory mechanisms. Then, offering combined therapy with these classes is more likely to produce additional CV benefits. SGLT-2i and GLP-1RA were shown in previous research to reduce macroalbuminuria, shorten serum creatinine doubling time, and slow the time to end-stage renal disease (14).

The present study attempted to investigate the impacts of adding SGLT-2i and GLP-1RA to the treatment of DM patients on their glycemic parameters and obesity status.

MATERIAL AND METHOD

The study was carried out with the permission of Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 02.19.2020, Decision No: 2019.12.04). We strictly followed the ethical rules and principles of the Declaration of Helsinki in all procedures of the study.

We recruited 42 diabetic patients applying to our internal medicine outpatient clinic to investigate the impacts of two new generation therapies, SGLT-2i and GLP1-RA, on weight. Six patients were excluded from follow-up for various reasons, and the study was finalized with 36 patients. The study design is retrospective cohort study, and the drug treatments were physician's choice.

We followed up on the patients' weight changes (i.e., body mass index; BMI), HbA1c levels, fasting blood glucose levels, and insulin doses. We preferably utilized mixed insulins (degludec/aspart at most) in patients with reduced insulin or who continued insulin for any reason and insulin glargine in patients using GLP-1RA.

Inclusion Criteria

- Being older than 18 years,
- Being diagnosed with T2DM,
- Being obese (according to BMI).

Exclusion Criteria

- Being without a malignancy diagnosis,
- Being younger than 18 years,
- Being diagnosed with the other types of DM except for T2DM.

Statistical Analysis

We reported to the results of the Shapiro-Wilk test and histograms to check the normality of distribution. Of the continuous variables, those with a normal distribution are presented as mean and standard deviation, while those deviating from a normal distribution are shown as median (minimum-maximum), and categorical variables are expressed as numbers and percentages. Accordingly, we performed a paired samples t-test and Wilcoxon signed-rank test to compare pre and post-treatment values of the patients. All statistical analyses were performed using SPSS 25.0 (Statistical Package for Social Sciences, Inc., Chicago, IL, USA), and a p-value <0.05 was accepted as statistically significant.

RESULTS

We found the mean age of the participants to be 60.4±8.4 years. The findings revealed that 18 patients lost weight compared to their initial weight, left their insulin treatment, and had a decreased HbA1c level. Although insulin was stopped in 2 patients, and they lost weight, we discovered that their HbA1c levels did not drop at the end of the study. Besides, we realized eight patients also had no decrease in their HbA1c levels despite weight loss and reduced insulin. However, the other eight patients had decreased HbA1c levels, lost weight, and had reduced insulin at the end of the study (**Table 1**).

Table 1. Patients' HbA1c levels and total insulin doses

	Insulin cessation (n=20)	Reduced insulin (n=16)
Reduced HbA1c level	18	8
Unreduced HbA1c level	2	8

Six patients included in the study were excluded from follow-up for various reasons.

The number of females discontinuing insulin therapy was more than that of males. While insulin was stopped in 15 (65.2%) female patients, 8 (34.7%) continued with reduced doses. These numbers were recorded as 5 (38.4%) and 8 (61.5%), respectively, among the male patients (**Table 2**).

Table 2. Patients' sex distribution by insulin status

	Insulin cessation (n=20)	Reduced insulin (n=16)
Male (n=13)	5	8
Female (n=23)	15	8

While SGLT-2i was added to the treatment of all patients, only 20 patients received additional GLP-1 RA. We discovered that GLP-1 RA was not initialized for any reason among ten patients without a decrease in their HbA1c levels.

We found the mean age to be lower among those discontinuing insulin; however, it was not statistically significant (p=0.278) (**Table 3**).

Table 3. Patients' age distribution by HbA1c change

	Mean Age
Insulin cessation & reduced HbA1c	58.9 years
Insulin cessation & unreduced HbA1c	64 years
Reduced insulin & reduced HbA1c	62.25 years
Reduced insulin & unreduced HbA1c	60.2 years

We determined that 20 patients whose insulin therapy was stopped continued their treatment with metformin, SGLT-2i, DPP-4 inhibitor, or GLP-1RA. Despite the use of SGLT-2i in all patients, no urinary or genital infection was detected to cause cessation of their treatment. During the follow-ups, the mean HbA1c level of the patients that discontinued insulin was found to be significantly lower than those containing insulin therapy (median 9.2 vs 7.4, $p < 0.001$).

The mean BMI value was determined to be significantly lower among the patients with insulin cessation than among their counterparts (median 39.2 vs 38.5 kg/m², p=0.003).

Two patients with insulin cessation but unreduced HbA1c (even increased) had higher BMI levels than those with reduced HbA1c (**Table 4**).

Table 4. BMI changes of patients with insulin cessation and unreduced HbA1c

	First follow-up	Sixth-month follow-up
1-	38.4	41.2
2-	39.7	42.3

We detected an increase in BMI values of 8 patients with a reduced insulin dose and an unreduced HbA1c level (p=0.012) (**Table 5**).

Table 5. BMI changes of patients with reduced insulin and unreduced HbA1c

	First follow-up	Sixth-month follow-up
1-	31.1	31.8
2-	33.2	34
3-	36	37
4-	35.8	36.2
5-	37.4	38.1
6-	30.6	31.8
7-	36.7	38.2
8-	38.2	39.1

Finally, we found a decrease in BMI values in patients with a reduced insulin dose and a more regulated blood glucose value, and thus, a reduced HbA1c level (**Table 6**).

Table 6. BMI changes of patients with reduced insulin and HbA1c

	First follow-up	Sixth-month follow-up
1-	52.5	50.6
2-	40.4	38.1
3-	42.1	40.3
4-	49.7	42.7
5-	39.8	38.8
6-	38.3	38.1
7-	41.6	40.4
8-	40	38.3

DISCUSSION

Our findings demonstrated that the mean HbA1c value of 20 patients with insulin cessation was 9.13% (min-max: 6.4-14) at the beginning of the treatment, while it was 7.63% (min-max: 5.2-10.8) in the sixth month of treatment modification. No serious side effects or adverse events were detected in the patients. Among these patients, two had a slight increase in their HbA1c levels, but we found a significant HbA1c decrease in 18 patients. In total, these 20 patients had an average of 1.5% HbA1c reduction. In addition, the mean BMI value of these 20 patients was found to be 38.99 kg/m² (min-max: 33.2-43.4), and the patients were Class 2 obese before the treatment modification. In the sixth month of treatment modification, it significantly decreased (0.86) and was calculated to be 38.13 kg/m², although there was a significant increase in the two patients' values.

In their study, Chen Li et al. (15) reviewed the data of 1,895 T2DM patients within eight papers. Accordingly, compared to monotherapy, combination therapy yielded a significant reduction in HbA1c, body weight, fasting plasma glucose, 2-hour postprandial glucose, systolic blood pressure, and BMI and caused no serious side effects in patients. The reduction in LDL cholesterol, HbA1c, body weight, and fasting blood glucose (FPG) persisted for more than one year, but these positive effects gradually receded over time.

Despite insulin cessation, two patients with an increased BMI value (M=2.7) at the sixth-month follow-up were older (about 65 years of age). In addition, HbA1c values increased from 6.8% to 7.8% in these patients. These findings may have arisen from non-compliance with treatment, and insulin cessation despite weight gain suggests that some patients may have started insulin earlier than others.

There is a paucity of research on whether older adult diabetics benefit from insulin administration training. Gumussoy et al. (16) reported that erroneous insulin use may affect glycemic control in older adult diabetic patients. In their study, 112 diabetic patients over 65 years (M=71.85±6.36 years) were given insulin administration training after being evaluated with the "Insulin-Treated Diabetes Mellitus Assessment Form." Four weeks later, insulin administration was re-evaluated among the patients. Although 76.8% of the patients had received such training before, all the participants were discovered to make a mistake in at least one of the insulin administration steps. However, the scholars found a significant improvement in the patients' erroneous insulin administration following the training. They also noted that the training may need to be repeated at regular intervals to ensure the permanency of correct insulin administration.

Insulin dose was reduced, and HbA1c levels decreased in eight patients at the end of the study. Besides, we found these patients' mean BMI value to be 43.05 kg/m² (min-max: 38.3-52.5) at the beginning of the treatment, while it became 40.91 (min-max: 38.1-50.6) in the sixth month of the treatment. In this case, it is evident that weight loss contributes to blood glucose regulation.

When it comes to eight patients with reduced insulin but unreduced HbA1c, the mean BMI value was recorded to be 34.87 kg/m² (min-max: 30.6-38.2) at the beginning of the treatment, but it increased to 35.77 kg/2 (min-max: 31.8-39.1) in the sixth month of the treatment modification. Despite no significant increase in HbA1c levels in these patients, a noteworthy reduction in insulin dose suggests that the patients may have used more insulin than necessary.

A randomized controlled trial of 9,340 patients with a median follow-up of 3.8 years compared liraglutide with a placebo. Fewer patients died from CV causes in the liraglutide group (n=219; 4.7%) than in the placebo group (n=278; 6.0) (OR, 0.78; 95% CI, 0.66 to 0.93; p=0.007). Moreover, the liraglutide group had insignificantly lower rates of non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure lower than the placebo group. The most common adverse events leading to liraglutide discontinuation were gastrointestinal events. In addition, the incidence of pancreatitis was found to be insignificantly lower in the liraglutide group than in the placebo group (17).

The literature hosts several large randomized controlled trials reporting statistically significant reductions in CV events in patients with T2DM treated with an SGLT-2i (empagliflozin, dapagliflozin, canagliflozin) or GLP-1 RA (exenatide, liraglutide, semaglutide). In diabetics with atherosclerotic cardiovascular disease (ACVD), empagliflozin reduced MACE and mortality compared to placebo. In our study, 42 patients (36 completed the study) were followed up for six months. All patients were using SGLT-2i, but only 20 were administered GLP-1 RA. Nevertheless, we detected no significant MACE in any of the patients.

In a cohort study recruiting 12,446 individuals to investigate the relationship between GLP-1 RA and SGLT-2i use and COVID-19 outcomes, the overall 60-day mortality rate was reported to be 3.11% (387 out of 12,446). It was 2.06% (138 out of 6,692) for GLP1-RA use, 2.32% (85 out of 3,665) for SGLT-2i use, and 5.67% (199 out of 3,511) for DPP4i use. Both GLP1-RA and SGLT-2i administration was associated with lower 60-day mortality compared to DPP4i use alone (OR 0.54 [95% CI 0.37-0.80] and 0.66 [0.50-0.86], respectively) (18).

In their study with 89 patients, Suhrie et al. (19) found the mean number of chronic medical conditions in older adult patients to be 8.4 and concluded that older adult patients were engaged in too much unnecessary medication. Therefore, and due to the high comorbidities, medication in older adults needs to be considered more.

SGLT-2i and GLP-1-RA are utilized as glucose-lowering therapies in T2DM patients, with additional benefits in weight loss and lowering blood pressure. CV outcome trials showed that these therapies protect against major CV disease in patients with ACVD, bring renoprotective benefits, reduce the risk of hospital admissions for heart failure, and decrease CV and all-cause mortality (20, 21). Although the above findings were not statistically measured in this study, we had similar observations in our patient cohort.

GLP-1RA and SGLT-2i are recommended for all patients with tolerable obesity and without a contraindicated condition (22).

The study has several limitations. Sample size was quite small, the patients are heterogenous, the measures of some parameters such as blood pressure, regular follow-up of lipid profiles were lack. The focus was on weight and glucose regulation, there are limited assessment about cardiovascular protection. Since retrospective design nature, some records were unavailable.

CONCLUSION

The introduction of SGLT-2i and GLP-1RA has strengthened our hand in treating T2DM patients, most of whom are obese. Since this patient group is often middle-aged, and because these two groups of medicines, which do not cause hypoglycemia, are more efficient on postprandial blood glucose and have significant benefits in both CV protection and weight control, we believe that they need to be deployed in particularly obese and contraindication-free patients and even to be a part of the treatment of only obese diabetics.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 02.19.2020, Decision No: 2019.12.04).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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